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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,223	10/18/2001	George Q. Daley	13086-002001	7405

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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,223	DALEY ET AL.	
	Examiner	Art Unit	maf
	Walter Schlapkohl	1636	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,24-26 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,24-26 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 11/16/2005 in which claim 47 was canceled and claims 1 and 26 were amended. Claims 1-12, 24-26 and 34-36 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, and therefore dependent claims 2-12, 24-26 and 34-36, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by Applicant's amendment.**

Claim 1 recites "[a] vector comprising from 5′ to 3′: a) a packaging sequence; b) a heterologous insert sequence or restriction sites for insertion of a heterologous sequence; and c) a 3′ long terminal repeat (LTR) sequence consisting of a rare cutter site selected from the groups consisting of: a Not1 site,

a SfiI site, a PacI site, a P1-SceI site and combinations thereof, wherein at least two codons of the packaging sequence are altered so as to reduce formation of fusion polypeptides encoded by the packaging sequence or a portion thereof, and the heterologous insert sequence" in lines 1-10. "Consisting of" is "closed" language and excludes the inclusion of any other LTR elements such as the direct repeat sequences, as well as the U3, R and U5 sequences described throughout the specification. Therefore, claim 1 is vague and indefinite in that it is unclear how a 3' LTR sequence can consist of only a rare cutter site or even a combination of rare cutter sites. According to Lewin (Genes V, Oxford University Press Inc., Chapter 35, pages 1033-1056, 1994) LTRs are direct repeat sequences at the ends of retroviruses/retroviral vectors which contain U3, R, and U5 subsequence domains (see especially pages 1038-1039 and Figure 35.5). Does Applicant intend an LTR sequence comprising a rare restriction site, wherein the restriction sites are limited to Not1, SfiI, PacI, P1-SceI sites or combinations thereof, or does Applicant intend that the LTR sequence is replaced by such a restriction site?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsman et al (US Patent 6,235,522; of record) in view of Eglitis et al (US Patent 5,672,510). **This is a new rejection necessitated by Applicant's amendment.**

Note: in order to expedite prosecution and for purposes of this rejection only, Examiner has interpreted claim 1 as a vector comprising a 3' LTR comprising a rare cutter site, wherein the cutter site is limited to a NotI site, an SfiI site, a PacI site, a P1-SceI site, or combinations thereof.

Kingsman et al teach a retroviral vector comprising a 5' LTR, a portion of the HIV1 *gag* packaging sequence gene (specifically nucleotides 791-1143 of the full length sequence, which corresponds to the amino-terminal region of HIV *gag*) altered at its three ATG codons (including the *gag* initiator codon), a multicloning site (comprising a number of restriction

sites for the insertion of a heterologous gene), and a 3' LTR (i.e., a proviral recovery sequence) (see for example, Figure 3, in combination with column 7, lines 53-58, and column 9, line 43). Importantly, Kingsman et al teach that the 3' LTR region used in their vector has been designed to contain several convenient restriction sites in order to allow the easy replacement/swapping of different promoter elements into the LTR (see for example, column 7, lines 23-26). Kingsman et al also teach using the amino terminal portion of the *gag* sequence, wherein the amino terminal portion of the *gag* sequence is altered in at least two codons. Additionally, Kingsman et al teach the alteration of all three of the nucleotides of the initiation codon (ATG->TAA; see SEQ ID NO: 1, residues 21-23, at column 8, lines 15-16). Finally, Kingsman et al teach that a heterologous insert sequence can be cloned into the vector (see for example column 4, lines 18-40) for gene therapy or marker expression purposes.

As it regards claim 6, it is noted that "a portion of the nucleotide sequence of SEQ ID NO: 2" is any nucleic acid thereof, such as adenine; the vector taught by Kingsman et al comprises adenine, and therefore the patent of Kingsman et al meets the limitation of claim 6.

As it regards claims 8-10, it is important to note that there is no specific sequence requirement for the claim; i.e., the claim does not require that the packaging sequence is SEQ ID NO: 1 having an altered codon sequence at positions 1097-1099 and/or 1589-1591. Rather, the limitation only requires that a sequence corresponding to 1097-1099 and/or 1589-1591 be altered from an ATG. Effectively, this can be interpreted as any sequence that lines up to 1097-1099 and/or 1589-1591 of SEQ ID NO: 1, and wherein the corresponding sequence in each position is not ATG, because the relationship in lining up the sequences is arbitrary within the limitations of the claim. Because the HIV *gag* sequence taught by Kingsman et al can line up with SEQ ID NO: 1 in various embodiments where the corresponding positions at 1097-1099 and/or 1589-1591 are not ATG, this limitation is also taught by Kingsman et al.

Although the Kingsman et al reference meets all of the limitations set forth above, Kingsman et al do not specifically teach the use of NotI, SfiI, PacI or P1-SceI as the restriction sites in the 3′ LTR region.

Eglitis et al teach that rarely occurring cleavage sites such as those for NotI are used for altering promoter sequences within the 3′ LTR of a retroviral vector (see entire document, especially column 4, lines 6-10 and lines 28-53). Eglitis et al

specifically teach that the use of such rare restriction sites "enables one to extract a first gene from the retroviral vector, and replace the first gene with a second gene without altering the retroviral vector backbone structure" (column 3, lines 60-65).

It would have been obvious for one of ordinary skill in the art to use the NotI site of Eglitis et al in the 3′ LTR region of the vector taught by Kingsman et al because Kingsman et al specifically teach that engineering the 3′ LTR region of the vector to contain restriction sites useful for cloning of alternative promoters is desirable, and Eglitis et al teach that rarely occurring cleavage sites such as those for NotI can be used to cut out cloned DNA from a vector without altering the vector backbone sequence.

The artisan of ordinary skill would have been motivated to place such a restriction site in the 3′ LTR of the vector taught by Kingsman et al, because Kingsman et al teach that the 3′ LTR region used in their vector has been designed to contain several convenient restriction sites in order to allow the easy replacement/swapping of different promoter elements into the LTR and Eglitis et al specifically teach the use of "rare" restriction enzymes such as NotI for use in altering the promoter in a 3′ LTR of a retroviral vector and that, further,

the use of such a "rare" site enables one to extract a first gene from the retroviral vector, and replace the first gene with a second gene without altering the retroviral vector backbone structure.

Based upon the teachings of the cited references, the skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success when combining the teachings of Kingsman et al and Eglitis et al.

Claims 1-12, 24-26 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kingsman et al and Eglitis et al (as applied to claims 1-12 above), and further in view of Beach et al (US Patent 6,025,192, of record).

Note: in order to expedite prosecution and for purposes of this rejection only, Examiner has interpreted claim 1 as a vector comprising a 3' LTR comprising a rare cutter site, wherein the cutter site is limited to a NotI site, an SfiI site, a PacI site, a P1-SceI site, and combinations thereof.

Kingsman et al and Eglitis et al disclose the limitations as set forth above in the rejection of claims 1-12 under 35 U.S.C. §103(a). Briefly, Kingsman et al and Eglitis et al teach a vector comprising a packaging sequence, a cloning site, and a

3' LTR comprising a rare cutter site, wherein the cutter site is limited to a NotI site, an SfiI site, a PacI site, a P1-SceI site, or combinations thereof.

However, Kingsman et al and Eglitis et al do not specifically disclose the inclusion of a bacterial origin of replication and bacterial selection marker (i.e., replicon) in their vector.

Beach et al teach a viral vector construct comprising a 3' LTR sequence comprising a proviral excision element, a packaging signal and a bacterial replicon comprising an origin or replication and a selection marker (see for example column 3, lines 33-46). Beach et al also teach that any bacterial selection marker can be used (see for example, column 5, lines 1-18). Beach et al further teach that, when in the context of a proviral excision element, the proviral excision element along with the bacterial origin or replication and the bacterial selectable marker can be recovered (along with desired genomic sequences) to yield a plasmid capable of replication in bacteria. Beach et al note that this is made possible by the presence of a bacterial origin of replication and a bacterial selectable marker within the isolated sequence (column 16, lines 6-12).

It would have been obvious for the skilled artisan to combine these teachings to construct a vector with a bacterial replicon further comprising a bacterial marker sequence because Beach et al teach that the proviral excision element of such a vector can be recovered and circularized to yield a plasmid capable of replication in bacteria.

The ordinary skilled artisan would have been motivated to combine the teachings of Kingsman et al and Eglitis et al with the teachings of Beach et al in order to create a vector that contains a bacterial replicon and thus can be produced in large quantities by using bacteria.

Absent evidence to the contrary, one of ordinary skill in the art would have had a reasonable expectation of success when combining the teachings of Kingsman et al and Eglitis et al with the teachings of Beach et al.

Claims 1-12, 24-26 and 34-36 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kingsman and Eglitis (as applied to claims 1-12, 24-25 and 35-36 above), and further in view of Ohi et al (US Patent 5,683,893).

Note: in order to expedite prosecution and for purposes of this rejection only, Examiner has interpreted claim 1 as a vector comprising a 3′ LTR comprising a rare cutter site,

wherein the cutter site is limited to a NotI site, an SfiI site, a PacI site, a P1-SceI site, and combinations thereof.

Kingsman et al, Eglitis et al and Beach et al disclose the limitations as set forth above in the rejection of claims 1-12, 24-26 and 35-36 under 35 U.S.C. §103(a). Briefly, Kingsman et al, Eglitis et al and Beach et al teach a vector comprising a packaging sequence, a cloning site, and a 3' LTR comprising a rare cutter site, wherein the cutter site is limited to a NotI site, an SfiI site, a PacI site, a P1-SceI site, or combinations thereof. Kingsman et al, Eglitis et al and Beach et al further teach such a vector including a bacterial origin of replication and a bacterial selection marker (i.e., replicon).

However, Kingsman et al, Eglitis et al and Beach et al do not specifically disclose such a vector wherein the selection marker is bleomycin.

Ohi et al teach a vector construct comprising a mutant AOX2 promoter and a bleomycin selection marker (see entire document, especially column 5, lines 44-50 and column 6, lines 10-20). Ohi et al also teach that the bleomycin selection marker, alone or in combination with other suitable selection markers, can be incorporated into suitable sites within the vector (column 6, lines 19-20).

It would have been obvious for the skilled artisan to combine these teachings to construct a vector comprising a 3' LTR comprising a rare cutter site, wherein the cutter site is limited to a NotI site, an SfiI site, a PacI site, a P1-SceI site, and combinations thereof with a bleomycin resistance marker because Beach et al teach that any bacterial selection marker can be used in such a vector and Ohi et al teach that bleomycin is a bacterial selection marker.

The ordinary skilled artisan would have been motivated to combine the teachings of Kingsman et al, Eglitis et al, and Beach et al with the teachings of Ohi et al in order to create a vector that contains a bleomycin bacterial marker that can be produced in large quantities by using bacteria.

Absent evidence to the contrary, one of ordinary skill in the art would have had a reasonable expectation of success when combining the teachings of Kingsman et al, Eglitis et al, and Beach et al with the teachings of Ohi et al.

Response to Arguments

Because all the rejections are new, Applicant's arguments have been rendered moot.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is sent to expire THREE MONTHS from the mailing date of this action. IN the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shorted statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period fro reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax

telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should

be directed to Walter A. Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

January 31, 2006

NANCY VOGEL, PH.D.
PATENT EXAMINER